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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,792	03/30/2004	Georges Belfort	18001/5062 (RPI-806)	4213

7590 02/20/2007

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EXAMINER	
BAUGHMAN, MOLLY E	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,792	BELFORT ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-62* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Applicant's election with traverse of Group I, Claims 1-10, 11 in part, 12-17, 203-37, 38 in part, 39-44, 47-53, 54 in part, and 55-60 in the reply filed on 1/24/2006 is acknowledged. The traversal is on the ground(s) that the claims of the present application are closely related and therefore, require common areas of search and consideration. Upon further consideration, the restriction has been withdrawn and all claims are currently under examination.

Claim Objections

2. Claim 3 is objected to because of the following informalities: the claim depends upon itself. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 28 is confusing because it cannot be determined what is encompassed by "whereby the target entity in the permeate is greater than 90% of the target entity present in the polydisperse liquid and the target entity is present in the permeate in a concentration of 7-20%." The phrase as written is confusing because it appears that the amount of target entity in the permeate has

increased from what was originally present in the polydisperse liquid. Furthermore, it is unclear what percentage of concentration the target entity is in reference to and therefore, the target entity's concentration in the permeate is unclear.

b. Claim 29 is confusing because it cannot be determined what is encompassed by "a *carved* microporous walled channel membrane." Claim 2 refers to "curved," and it is unclear whether this is a typo or whether it refers to a different membrane.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-2, 4,7, 8, 11-17, 28-29, 31, 34-35, and 38-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Kopf et al. (U.S. 6,875,459).

Kopf et al. discuss a method of filtering various components and subcomponents of milk using cross-flow filtration devices, which can be microfiltration, ultrafiltration, nanofiltration and reverse osmosis filter systems (column 3 lines 45-50, and column 8, lines 38-65). During the process, the source is subjected to a microfiltration membrane, allows the targets to flow through into the permeate and separate from the solids or high-molecular weight species, and then the permeate is subjected to an ultrafiltration

membrane where it captures the target (column 3, lines 23-60, and column 18, lines 37-48). The membranes can be in any format, such as hollow fibers, spirals, tubular and ceramic. Similarly, devices such as spirals are designed to maximize membrane utilization base on the width that membranes could be cast (column 10, lines 13-15; column 15, lines 9-12). In certain examples, it was observed that protein passage was above 90% (column 16, lines 2-5), and some proteins had a retentate yield of 100%, wherein the concentration of protein in the permeate was greater than 7% (Tables 2-6).

Such sources can be genetically engineered cell lines, milk, whey, juice, mammalian cells, antigens, antibodies, viral particles, plant or tissue extracts, immunoglobulins, albumins, IgG, carbohydrates, peptides, lactose, bovine serum albumin, lactose, lactoperoxidase, blood clotting Factor VIII, proteins, hormones, monoclonal antibodies, glycomacropeptide (GMP), Siallyllactose, of which can be from a transgenic or hyper-immunized mammal (column 4, lines 29-31, 45-49; column 6, lines 48-51, 59-60; column 17, lines 1-5, 30-31; column 18, line 38; column 19, lines 49-58).

The reaction should be performed with cross flow velocities and channel velocities between 0.5 and 2.5 m/sec (column 13, lines 13-25), flow velocity between 32-40 lm^2h, depending on the membrane (Tables 2-5).

7. Claims 48-49, 52, 54-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Menon et al, "Effect of Ion Binding on Protein transport through

Ultrafiltration membranes," Biotechnology and Engineering, May 1999, Vol. 63, No.3., pp. 298-307.

Menon et al. discuss quantifying the effects of specific ions on protein transport through semipermeable ultrafiltration membranes over a range of solution pH and salt concentrations. In their experiments, they first test filtering BSA at a range of pH values from pH 3-7, where the NaCl concentration is 10 mM (page 300, Figure 1). At a pH's above 4.8, BSA's isoelectric point, they showed a decrease in sieving coefficient, due to the repulsive electrostatic interaction between charged protein and the pore boundary (page 301, 2nd paragraph and Figure 3). In another experiment, Menon describes the separation of albumin and immunoglobulin G by lowering the pH to 4.8 (near the isoelectric point of albumin), and reducing the salt concentration to 1.5mM, wherein the positively charged immunoglobulins are rejected by the membrane while the uncharged BSA is passed relatively easily (page 298-299).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 3 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf et al. (U.S. 6,875,459) as applied to claims 1-2, 4,7, 8, 11-17, 28-29, 31, 34-35, and 38-44 above, and further in view of Dzengleski et al. (U.S. 6,824,679).

The teachings of Kopf et al. are discussed above. Kopf does not discuss the use of a helical hollow fiber membrane module which produces Dean vortices of sufficient strength in the microfiltration process.

Dzengleski et al. describe the use of a multi-layered coiled hollow fiber bundle in a separation module, the bundle comprising a plurality of coiled hollow fibers that form the outline of concentric circles such that when subjected to a fluid of a certain velocity, Dean vortices are created (column 6, lines 35-55 and Figure 10). The hollow fibers are characterized by a set of variables including the length of a mandrel around which the fiber bundle will be coiled (column 7, lines 10-25).

Such a separation module can be used in ultrafiltration, microfiltration, or nanofiltration, such that transgenic milk, lysed cell broths, albumin, mammalian cells, bacterial cells, gene therapy plasmids, and biotech products can be filtered for targets such as proteins, antibiotics, DNA, RNA, ribozymes, proteins, enzymes, hormones,

antibiotics and peptides (column 4, lines 10-60, Column 9, lines 36-47,column 12, lines 40-48).

Permeate flux and transmembrane pressure are calculated in respect to permeate and retentate pressure, wherein such values could be 20 lmh (permeation flux) and transmembrane pressure values < 2 psi depending on membrane loading (Figure 8 – y axis, column 13, lines 46-55, column 15, lines 38-45). Axial flow rate can be < 1 m/s (see Table III).

One of ordinary skill in the art would have been motivated to modify the method of Kopf et al. to use helical hollow fiber membrane module which produces Dean vortices because Dzengleski et al. states the benefits of such a coiled hollow fibers are that they benefit from the de-fouling properties of Dean vortices, and have substantially equivalent performance characteristics that are predictable (column 2). The skilled artisan would have had a reasonable expectation of success in using a helical hollow fiber membrane module which produces Dean vortices of sufficient strength in the microfiltration process in the method of Kopf et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed helical hollow fiber membrane module therein.

11. Claims 6, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf et al. (U.S. 6,875,459).

The teachings of Kopf are discussed above. Although Kopf does not particularly state carrying out the microfiltration process at a transmembrane pressure different less

than 2 psi, Kopf states that the end user should assay the passage of the target material at TMP's between 2 and 15 PSI, where cross-flow velocity is optimized between 0.5 and 2.5 m/sec for devices with channel heights between 0.5 mm and 1.5 mm (column 14, lines 54-58).

One of ordinary skill in the art would have been motivated to modify the method of Kopf et al. to carrying out the microfiltration process at a transmembrane pressure different less than 2 psi because Kopf demonstrates that it is necessary to optimize the transmembrane pressure (TMP) after appropriate tangential velocity has been determined in order to define the correlation of TMP to permeate flow rate, which ultimately depends on the cross-flow velocity and channel height of the microfiltration device (column 14, lines 15-58). The skilled artisan would have had a reasonable expectation of success in carrying out the microfiltration process at a transmembrane pressure different less than 2 psi of Kopf et al. It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the transmembrane pressure different less than 2 psi therein.

Thus, an ordinary practitioner would have recognized that the transmembrane pressure difference could be adjusted to maximize the desired results. As noted in In re Aller, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific concentrations was other than routine, that the products resulting from the optimization have any unexpected properties, or that the

results should be considered unexpected in any way as compared to the closest prior art.

12. Claims 5, 10, 21-26, 32, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf et al. (U.S. 6,875,459) as applied to claims 1-2, 4,7, 8, 11-17, 28-29, 31, 34-35, and 38-44 above, and further in view of Menon et al, "Effect of Ion Binding on Protein transport through Ultrafiltration membranes," Biotechnology and Engineering, May 1999, Vol. 63, No.3., pp. 298-307.

The teachings of Kopf et al. are discussed above. Kopf does not discuss the microfiltration process carried out at the target entity's isoelectric pH [claims 5, 32, and 37]. Kopf also does not discuss the ultrafiltration process carried out by utilizing an ultrafiltration membrane under conditions effective to permit the target entity to be retained on the ultrafiltration membrane at a pH which differs from the target entity's pI [claim 21], or wherein the pH is above that at which the target entity precipitates [claim 22], or wherein the pH is greater than 8.5 [claim 23], or wherein the pH is greater than 10 [claim 24]. Kopf does not discuss the ultrafiltration process carried out at an ionic strength of 10-20 mM NaCl [claim 25], or wherein the ionic strength is between 12-17 mM NaCl [claim 26].

Menon et al., as discussed above, describe quantifying the effects of specific ions on protein transport through semipermeable ultrafiltration membranes over a range of solution pH and salt concentrations. Menon describes the separation of albumin and immunoglobulin G by lowering the pH to 4.8 (near the isoelectric point of albumin), and reducing the salt concentration to 1.5mM, wherein the positively charged

immunoglobulins are rejected by the membrane while the uncharged BSA is passed relatively easily (page 298-299). Menon also discusses the use of NaCl concentrations between 3 mM to 450 mM (page 303, and Figure 4).

One of ordinary skill in the art would have been motivated to modify the method of Kopf et al. to carry out the microfiltration process at the target entity's isoelectric pH, and the ultrafiltration at a pH which differs from the target entity's pI, particularly at pH values above 8.5, or even above 10 because Menon et al. demonstrate that the rate of protein transport through semi-permeable membranes is strongly affected by solution pH and ionic strength, wherein a pH above or below the isoelectric point causes repulsive electrostatic interaction between the charged protein and the pore boundary [i.e. a pH furthest above or below would cause the most repulsion] (page 301, 2nd paragraph, page 306, Conclusions). One of ordinary skill in the art would have been motivated to modify the method of Kopf et al. to carry out the ultrafiltration process with an ionic strength between 12-17 mM NaCl because Menon states that "the variety and specificity of ion binding interactions suggest that the extent of ion binding could potentially be used to vary the protein charge in a well-defined manner, providing an opportunity to alter protein sieving coefficients and significantly enhance the selectivity of membrane systems for protein separations" (page 306, 1st column, 2nd paragraph).

Thus, the skilled artisan would have had a reasonable expectation of success in carrying out the microfiltration process at the target entity's isoelectric pH, carrying out the ultrafiltration at a pH which differs from the target entity's pI, particularly at pH values

above 8.5, or even above 10, and carrying out the ultrafiltration process with an ionic strength between 12-17 mM NaCl in the method of Kopf et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed target entity's isoelectric pH during microfiltration and ultrafiltration process with pH values above 8.5 or even above 10, as well as an ionic strength between 12-17 mM NaCl therein.

13. Claims 9, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf et al. (U.S. 6,875,459) in view of Dzengleski et al. (U.S. 6,824,679), and further in view of Menon et al, "Effect of Ion Binding on Protein transport through Ultrafiltration membranes," Biotechnology and Engineering, May 1999, Vol. 63, No.3., pp. 298-307.

The teachings of the primary references are discussed above. These references do not discuss the microfiltration process of Claim 9 carried out at the target entity's isoelectric pH.

The teachings of Menon are discussed above, specifically Menon discusses how positively charged immunoglobulins are rejected by the membrane while the uncharged BSA is passed relatively easily when carrying out the filtration process at BSA's isoelectric pH.

One of ordinary skill in the art would have been motivated to modify the method of Kopf et al. and Dzengleski et al. to carry out the microfiltration process of Claim 9 at the target entity's isoelectric pH because Menon et al. demonstrate that the rate of protein transport through semi-permeable membranes is strongly affected by solution

pH and ionic strength, wherein a pH above or below the isoelectric point causes repulsive electrostatic interaction between the charged protein and the pore boundary (page 301, 2nd paragraph, page 306, Conclusions). The skilled artisan would have had a reasonable expectation of success in carrying out the microfiltration process at the target entity's isoelectric pH in the method of Kopf et al. and Dzengleski et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed target entity's isoelectric pH during microfiltration therein.

14. Claims 18-19 and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf et al. (U.S. 6,875,459) as applied to claims 1-2, 4,7, 8, 11-17, 28-29, 31, 34-35, and 38-44 above, and further in view of Oishi et al. (U.S. 2003/0033637).

The teachings of Kopf et al. are discussed above. Although Kopf discusses using sources from plant or tissue extracts and transgenic mammals, Kopf does not particularly describe using a polydisperse liquid being a cell culture fluid from transgenic plants cells.

Oishi et al. describe cultivating transformed or transfected plant or plant cell culture under conditions that result in the expression of TGF-beta proteins in the plant host system. The invention also contemplates a plant, plant cell culture, or plant seed transformed with the chimeric nucleic acid sequence of the invention (page 3, [0017]). Figure 6 shows western blot analysis of a protein produced from transgenic tobacco

plants (page 3, Brief Description of the Drawings). In Example 2, Oishi demonstrates that it is necessary to purify the tobacco preparations before experimentation, wherein they submitted the samples to ultrafiltration or microfiltration (page 16-17, [0167-0168] and Table 1).

One of ordinary skill in the art would have been motivated to modify the method of Kopf et al. to use a polydisperse liquid that is cell culture fluid from transgenic plant cells because the benefits of using microfiltration or ultrafiltration to purify proteins from transgenic tobacco plant cell cultures was shown by Oishi et al. The skilled -artisan would have had a reasonable expectation of success in using a polydisperse liquid that is cell culture fluid from transgenic plant cells such as tobacco in the method of Kopf et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed cell culture fluid from transgenic tobacco cells therein.

15. Claims 20 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf et al. (U.S. 6,875,459) as applied to claims 1-2, 4,7, 8, 11-17, 28-29, 31, 34-35, and 38-44 above, and further in view of Luque et al., "A New Coiled Hollow-Fiber Module Design for Enhanced Microfiltration Performance in Biotechnology," Biotechnology and Bioengineering, Nov.1999, Vol.65, No.3, pp.247-257.

The teachings of Kopf et al. are discussed above. Kopf does not discuss subjecting the microfiltration membrane to an acid-free cleaning regime after said subjecting the polydisperse liquid to a microfiltration process.

Luque et al. discuss a method of subjecting various polydisperse liquids (i.e. yeast broth, E. Coli lysates, and Chinese Hamster Ovary cell lysates – page 249-250) to microfiltration, and after experimentation, rinsing the system thoroughly with deionized water, then flushing with beach solution at 49kPa (7 psi) (page 251-252, Cleaning Procedure).

One of ordinary skill in the art would have been motivated to modify the method of Kopf et al. to subjecting the microfiltration membrane to an acid-free cleaning regime after the microfiltration process because Luque et al. describe the benefits of cleaning the microfiltration system with an acid-free bleach solution following experimentation. The skilled artisan would have had a reasonable expectation of success in subjecting the microfiltration membrane to an acid-free cleaning regime after the microfiltration process in the method of Kopf et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed acid-free cleaning regime therein.

16. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf et al. (U.S. 6,875,459) as applied to claims 1-2, 4,7, 8, 11-17, 28-29, 31, 34-35, and 38-44 above, and further in view of Belfort et al. (U.S. 5,204,002).

The teachings of the Kopf are discussed above. Kopf does no discuss carrying out the ultrafiltration process at a permeation flux of 100-130 lmh.

Belfort et al. discuss the use of a curved channel filtration membrane with porous walls. Such a membrane can be microfiltration, ultrafiltration, nanofiltration, or reverse

osmosis membrane (see claim 15). The filtration apparatus separates at least one substance of a fluid, from another substance of the fluid, wherein the inner wall of material is porous to one substance and which is curved around an axis of curvature, the outer wall of material is porous to the one substance and which is curved around an axis of curvature, while being spaced outwardly of the inner wall by a gap defining a curved channel for the flow of fluid. The flow channel is permeable to at least one substance within the fluid (column 2, lines 14-30, 54-65). Figure 18 shows flux values between 100-130 lmh for the membranes with and without vortices.

One of ordinary skill in the art would have been motivated to modify the method of Kopf et al. to carry out the ultrafiltration process at permeation flux values of 100-130 lmh because Belfort demonstrates that it was common in the art to use ultrafiltration membranes which carry out ultrafiltration at such flux values. The skilled artisan would have had a reasonable expectation of success in carrying out the ultrafiltration process at permeation flux values of 100-130 lmh in the method of Kopf et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and the use the claimed permeation fluxes of 100-130 lmh therein.

17. Claims 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menon et al, "Effect of Ion Binding on Protein transport through Ultrafiltration membranes," Biotechnology and Engineering, May 1999, Vol. 63, No.3., pp. 298-307.

The teachings of Menon are discussed above. Although Menon does not particularly describe the ultrafiltration process carried out at a pH greater than 8.5 [claim 50], or at a pH greater than 10 [claim 51], Menon noted that at a pH's above 4.8, BSA's isoelectric point, there was a decrease in sieving coefficient, due to the repulsive electrostatic interaction between charged protein and the pore boundary (page 301, 2nd paragraph and Figure 3).

One of ordinary skill in the art would have been motivated to modify the method of Menon et al. to carry out the ultrafiltration at pH values above 8.5, or even above 10 because Menon et al. demonstrate that the rate of protein transport through semi-permeable membranes is strongly affected by solution pH and ionic strength, wherein a pH above or below the isoelectric point causes repulsive electrostatic interaction between the charged protein and the pore boundary [i.e. a pH furthest above or below would cause the most repulsion] (page 301, 2nd paragraph, page 306, Conclusions). The skilled artisan would have had a reasonable expectation of success in carrying out the ultrafiltration at pH values above 8.5, or even above 10 to ensure the target entity is retained on the membrane in the method of Menon et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed ultrafiltration process with pH values above 8.5 or even above 10 therein.

18. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Menon et al, "Effect of Ion Binding on Protein transport through Ultrafiltration membranes,"

Biotechnology and Engineering, May 1999, Vol. 63, No.3., pp. 298-307, as applied to claims 48-49, 52, 54-57 above, and further in view of Belfort et al. (U.S. 5,204,002).

The teachings of Menon et al. are discussed above. Menon does not describe the ultrafiltration process carried out at a permeation flux of 100-130 lmh.

Belfort et al. discuss the use of a curved channel filtration membrane with porous walls. Such a membrane can be microfiltration, ultrafiltration, nanofiltration, or reverse osmosis membrane (see claim 15). Figures 18 shows flux values between 100-130 lmh for the membranes with and without vortices.

One of ordinary skill in the art would have been motivated to modify the method of Menon et al. to carry out the ultrafiltration process at permeation flux values of 100-130 lmh because Belfort demonstrates that it was common in the art to use ultrafiltration membranes which carry out ultrafiltration at such flux values. The skilled artisan would have had a reasonable expectation of success in carrying out the ultrafiltration process at permeation flux values of 100-130 lmh in the method of Menon et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and the use the claimed permeation fluxes of 100-130 lmh therein.

19. Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menon et al, "Effect of Ion Binding on Protein transport through Ultrafiltration membranes," Biotechnology and Engineering, May 1999, Vol. 63, No.3., pp. 298-307 as

applied to claims 48-49, 52, 54, and 56-57 above, and further in view of Kopf et al. (U.S. 6,875,459).

The teachings of Menon et al. are discussed above. Menon does not discuss the ultrafiltration process wherein the protein or polypeptide is selected from the group consisting of alpha-proteinase inhibitor, alkaline phosphatase, angiogenin, antithrombin III, chitinase, extracellular superoxide dismutase, Factor VIII, Factor IX, Factor X, fibrinogen, glucocerebrosidase, glutamate decarboxylase, human serum albumin, insulin, myelin basic protein, lactoferrin, lactoglobulin, lysozyme, lactalbumin, proinsulin, soluble CD4, component and complex of soluble CD4, and tissue plaminogen activator [claim 58]. Menon does not discuss the ultrafiltration process where the polydisperse liquid is milk produced by a transgenic animal [claim 59], or wherein the transgenic animal is selected from the group consisting of a cow, goat, pig, rabbit, mouse, rat, and sheep [claim 60].

The teachings of Kopf are discussed above, particularly, Kopf discusses using sources can be genetically engineered cell lines, milk, whey, juice, mammalian cells, antigens, antibodies, viral particles, plant or tissue extracts, immunoglobulins, albumins, IgG, carbohydrates, peptides, lactose, bovine serum albumin, lactose, lactoperoxidase, blood clotting Factor VIII, proteins, hormones, monoclonal antibodies, glycomacropeptide (GMP), Siallyllactose, of which can be from a transgenic or hyper-immunized mammal (column 4, lines 29-31, 45-49; column 6, lines 48-51, 59-60; column 17, lines 1-5, 30-31; column 18, line 38; column 19, lines 49-58).

One of ordinary skill in the art would have been motivated to modify the method of Menon et al. to carry out the ultrafiltration process for a target entity which is Factor VIII, or where the polydisperse liquid is milk from a transgenic animal from a cow, goat, pig, rabbit, mouse, rat or sheep because the benefits of subjecting transgenic milk from lactating mammal to ultrafiltration in order to isolate proteins such as Factor VIII was shown by Kopf et al. The skilled artisan would have had a reasonable expectation of success in using the ultrafiltration process to isolate Factor VII from milk produced from a cow, goat, pig, rabbit, mouse, rat or sheep in the method of Menon et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed milk from a transgenic cow, goat, pig, rabbit, mouse, rat or sheep to isolate a protein such as Factor VIII therein.

20. Claims 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menon et al, "Effect of Ion Binding on Protein transport through Ultrafiltration membranes," Biotechnology and Engineering, May 1999, Vol. 63, No.3., pp. 298-307, as applied to claims 48-49, 52, 54-57 above, and further in view of Oishi et al. (U.S. 2003/0033637).

The teachings of Menon et al. are discussed above. Menon does not describe using the ultrafiltration process with cell culture fluid from transgenic plants cells.

Oishi et al. describe cultivating transformed or transfected plant or plant cell culture under conditions that result in the expression of TGF-beta proteins in the plant host system. The invention also contemplates a plant, plant cell culture, or plant seed

transformed with the chimeric nucleic acid sequence of the invention (page 3, [0017]). Figure 6 shows western blot analysis of a protein produced from transgenic tobacco plants (page 3, Brief Description of the Drawings). In Example 2, Oishi demonstrates that it is necessary to purify the tobacco preparations before experimentation, wherein they submitted the samples to ultrafiltration or microfiltration (page 16-17, [0167-0168] and Table 1).

One of ordinary skill in the art would have been motivated to modify the method of Menon et al. to carry out the ultrafiltration process where the polydisperse liquid is cell culture fluid from transgenic plant cells because the benefits of using ultrafiltration to purify proteins from transgenic tobacco plant cell cultures was shown by Oishi et al. The skilled artisan would have had a reasonable expectation of success in carry out the ultrafiltration process where the polydisperse liquid is cell culture fluid from transgenic plant cells such as tobacco in the method of Meon et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed cell culture fluid from transgenic tobacco cells therein.

SUMMARY

21. No claims are free of the prior art.

22. Brody, Ernest (U.S. 2003/0166866 A1) is noted as a reference of interest.

CONCLUSIONS

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

MEB 2/14/07

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

2/15/07